REMARKS

Status of the Claims

Claims 1-17 and 21-23 are pending; claims 18-20 have been withdrawn. Claims 1-14, 16 and 23 were rejected, and claims 15, 17, 21 and 22 were objected to.

Claim 1 has been amended to further limit L^1. The amendment is supported throughout the specification, and adds no new matter. It also is believed to place the claims in condition for allowance, as suggested by the acknowledged allowability of claim 21, in which L^1 is a C3-C6 alkylene or alkenylene chain. Entry of the amendment, and reconsideration in view of the following comments, are therefore requested.

The Examiner stated that the claims include non-elected subject matter. The Applicants have revisited the restriction requirement and the election, and can find nothing in the claims that is outside the scope of the Group that was elected. The Examiner may have relied upon a certain scope for searching, and stopped the search at a certain point upon finding Kuroita. However, that does not define the scope of the *election*, nor does the Applicant understand the basis for some of the limits mentioned in the previous office action, *e.g.*, limiting the linkers to C1-C5 groups as the Examiner indicated—indeed this limitation appears to be at odds with the acknowledgment that claim 21 is allowable. That limitation of the linkers is not drawn from the disclosure or based on any prior art limitations, and the Examiner has not alleged that such linkers are patentably distinct from the C1-C10 or C2-C10 linkers claimed. Accordingly, the Applicants have not further amended the claims based on the Examiner's statement about non-elected subject matter, but would invite and appreciate clarification of this issue.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-14, 16 and 23 were rejected as allegedly obvious, in view of a single reference, Kuroita. The Applicant traverses this rejection for reasons of record, which are further discussed below.

The Applicants greatly appreciate acknowledgment that claims 15, 17, and 21-22 would be allowable if written in independent form In an attempt to avoid filing an appeal, the Applicants have made an amendment to claim 1 that further distinguishes the claims from anything Kuroita discloses. Claim 1 has been amended to require L^1 to contain at least three linking atoms when W is L^2-A^3. This appears to overcome the art-based rejections, since claim 21 was acknowledged to be allowable and requires L^1 to be a C3-C6 alkylene or alkenylene. In view of the Amendment, the claims are believed to be allowable.

The rejection is traversed for reasons that have been discussed before: no *prima facie* case of obviousness has been established under the standards in, e.g., *Takeda v. Alphapharm*; and evidence of non-obviousness has been presented, to rebut any basis for alleging obviousness. Reconsideration of the rejection in view of the following remarks is respectfully requested, in the event the amendment is not found sufficient to overcome the outstanding rejection.

The Examiner asserted that hydrogen and methyl are "obvious variants as they are isotopes of the same element." That is a clear error of fact: Methyl is $-CH_3$, and it is not an isotope of hydrogen (H).

The Examiner cited In re Wood, saying that compounds with similar structures "are expected to have similar properties unless there is evidence on the record of secondary considerations." First, stating that such compounds are 'expected to have similar properties' does not say they are *prima facie* obvious. Second, the case certainly does not suggest that 'secondary considerations' as that term is used elsewhere, are required: evidence of non-obviousness takes many forms, and evidence of non-obviousness is present in the facts at issue here.

In re Wood has its own facts that must be recognized: it related to a situation in which the claimed compound had the same activity as the cited reference ("In view of the close structural similarity between the claimed compounds and Mitsuda compound III, cf. In re Hoke, 560 F.2d 436, 195 USPQ 148 (CCPA 1977); In re Lohr, supra, and the fact that the latter is disclosed as possessing antimicrobial activity, we believe that one skilled in the art would have been, prima

facie, motivated to make the claimed compounds in the expectation that they, too, would possess antimicrobial activity." And according to the case In re Woods, the reference apparently disclosed only three compounds. ("…with only the three compounds of the Mitsuda reference…" In re Wood at 141.) Neither of those facts is similar to the present case.

Moreover, *Takeda v Alphapharm* is a very recent Federal Circuit case, which specifically recognizes and rebuts the position that obviousness is established merely by finding a prior art compound with structural similarity, or one that can be called a homolog, isomer or analog. *Takeda* recognizes the same proposition on which the rejection relies, and discusses the leading cases on this point (it does not mention *Wood* specifically, but refers to similar cases, including *In re Deuel*, 51 F.3d 1552, 1558 [34 USPQ2d 1210] (Fed. Cir. 1995), "where we stated that '[n]ormally a prima facie case of obviousness is based upon structural similarity… A known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.' *Id.*)." *Immediately* after that statement, though, the Federal Circuit said this:

> We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 [21 USPQ2d 1941] (Fed. Cir. 1992); *Dillon*, 919 F.2d 688 [16 USPQ2d 1897] ; *Grabiak*, 769 F.2d 729 [226 USPQ 870]; *In re Lalu*, 747 F.2d 703 [223 USPQ 1257](Fed. Cir. 1984)).
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> That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*. [2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known

> compound in a particular manner to establish prima facie obviousness of a new claimed compound.

Takeda, 83 USPQ2d 1169, at 1174 (emphasis added).

Takeda was cited by the Applicant in the previous response, and it has not been rebutted by the Examiner. (The Examiner said that *Takeda* differed in two respects, but the Examiner focused on the facts of *Takeda* and did not rebut the clearly stated standards.) The final rejection continues to rely entirely upon a theory that it would have been obvious to select one specific compound from Kuroita, and to make one specific change to one specific position of that compound. The only basis for that proposed change is the Examiner's position that Methyl is an obvious variant of Hydrogen. *Takeda* discusses at great length how obviousness can or cannot be established, and it clearly indicates that 'structural similarity' alone, or merely being a homolog, isomer or analog of a prior art compound, is *just not enough* to establish prima facie obviousness. Note the underlined passages in the quotes above, where the Takeda court said "A known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties…" and *then* the court said that, nevertheless, "in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. And in *Takeda*, the prior art compound had the same asserted activity as the later claimed compound, which is not the case here; thus even if a *prima facie* case were established, which it has not been under the express standard in *Takeda*, it would be rebutted by evidence that the claimed invention has unexpected properties.

In *Takeda*, the court discussed a two step analysis for showing obviousness based on a prior art compound: would a person of ordinary skill have motivation to Select a particular compound from the prior art? And would the person of ordinary skill have had motivation to 'modify the compound in a particular manner' to arrive at the claimed invention? The Examiner has not established any reason to select the Kuroita compound on which the rejection relies: the reference apparently discloses at least 125 compounds (see columns 21-60 and the named compounds of examples 1-125 therein). The species the Examiner relies upon does not appear to be

singled out as one of special interest—it was selected solely based on the Applicant's disclosure from a myriad of possibilities. Other than depicting a specific structure in a list of such structures—which does not distinguish this fact pattern from the one in *Takeda,* where a specific structure was also disclosed in the reference—the Examiner has offered no reason to select the particular species from all disclosed in the reference.

Second question: Would a person of ordinary skill have reason to make the "the specific molecular modifications necessary to achieve the claimed invention" in this case? The Examiner's theory of obviousness requires putting a methyl group on a particular position of a compound from Kuroita. *Takeda* says that even if a claimed compound may be considered a homolog, isomer or analog of a prior art compound, it is still necessary to show that the prior art provides a reason to make particular structural changes. It is not enough to say hydrogen renders methyl obvious. That standard was not met here: the selection of the change to make *and* the selection of the place to make it were *both* done only by looking at the Applicants' disclosure.

Moreover, no compound in the reference shows that the particular position on which that substituent was added is capable of *tolerating* an added substituent at that position. Indeed, the relevant group in the reference compound appears to correspond to item (2) in a list of substructures that can be used as the R^1 group, and substructure (2) does not even *permit* a methyl group to be put there. That suggests that the reference did not consider such compounds to be obvious variants or to have the activity associated with the very broad genus that was described. Thus the reference does not support adding the Methyl group that the Examiner's theory requires. The Examiner has not cited a case showing that putting a methyl group where none was before supports a prima facie case of obviousness without more, or that it supports a conclusion of obviousness.

Nor has the Examiner offered any reason to select the particular position for modification. The large number of compounds in Kuroita offers an extremely large number of places where H could be replaced with methyl—no reason for the selection of either this compound or this change was provided.

In many of the cases where structural similarity is the basis for finding obviousness, the claimed compound exhibits the same activity as the prior art. That is not the case here. Nor does the prior art genus encompass what is now claimed, which might support the obviousness of the claimed compounds. Rather, the claimed genus does not overlap with the one in the prior art at all, and the prior art offers no reason to make what the Examiner proposed—other than the bare assertion that H and Methyl are obvious variants. Respectfully, *Takeda* emphasizes that this alone is not enough.

The Examiner stated that the courts have "consistently" found it obvious to replace H with a methyl group. No case was cited to support that proposition, which makes it difficult to rebut: however, the Applicant's are aware of no case where that alone justified a conclusion of obviousness. Obviousness is a conclusion based on all of the facts. Respectfully, most of the relevant case law appears to conclude that an adjacent homolog is *prima facie* obvious where it has the same activity as the prior art compound. *Takeda* makes it clear that merely identifying an isomer or homolog in the prior art is NOT sufficient to establish obviousness—at least not where the claimed compounds have activity that could not have been expected from the prior art, as is the case here. And where the claimed compounds have a different activity or use, even if a prima facie case were made at, it would not support a *conclusion* of obviousness.

Finally, the Examiner asserts that the disclosure "does not contain any unexpected results of the presently claimed compounds..." The Applicant strenuously disagrees. The disclosure shows activity for inhibition of calcium channel activity, and for treating conditions associated with calcium channel activity. Kuroita provides compounds having serotonin 2 receptor antagonistic and platelet aggregation suppressive actions, said to be useful for thrombotic embolism, dry eye and the like. (Kuroita's abstract.) The compounds of the present invention are shown to be useful for treating certain types of pain in particular: nothing in Kuroita suggests that compounds of the claimed structure could have that use. (The Applicant's representative is not aware of any such disclosure, and did a text search of the document in the PTO site for 'pain' without finding the word in the entire patent.)

This is not a case like *In re Wood*, where a claimed compound was considered obvious based on a structurally similar prior art compound with the same activity: the Applicants have made an important and inventive contribution, by discovering a genus of compounds useful for treating pain and other calcium channel-related disorders. The genus as claimed, even if it approaches what Kuroita discloses, should not be found unpatentable merely based on structural similarity. *Takeda* states—several times in a row—that more is needed than an assertion that the claimed compounds could be isomers, homologs or analogs of prior art compounds. Yet here, the Examiner's entire rationale for the "suggestion to make the change" is that changing H to Methyl is 'obvious' because of the structural similarity.

The Examiner concluded that "the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art." However, the claimed invention as a whole relates to a genus that bears little resemblance to Kuroita's compounds, and does not overlap with them at all. That genus possesses activity that could not have been expected from Kuroita's disclosure. A holding of obviousness is a conclusion that should be based on all of the facts; evidence of activity that could not have been predicted from the prior art supports a finding of non-obviousness. Thus even if *prima facie* obviousness were established, it would be rebutted by the evidence that the presently claimed genus provides a useful and valuable activity that was not known and could not have been predicted from the prior art.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 381092001600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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